PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTIBSOVO®

Ivosidenib Tablets

Tablets, 250 mg, Oral

Antineoplastic Agent

Servier Canada Inc.
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Laval, Quebec H7T 2S4
Canada

Date of Initial Authorization:
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Submission Control Number: 277139

RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

- TIBSOVO (ivosidenib) in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.

- TIBSOVO monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

  Documentation of an IDH1 R132 mutation using an appropriate diagnostic test is required prior to treatment with TIBSOVO.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in effectiveness or safety were observed between patients who were 65 years and older compared to younger patients (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, 14 CLINICAL TRIALS, 4 DOSAGE AND ADMINISTRATION)

2 CONTRAINDICATIONS

TIBSOVO is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)
- are taking strong CYP3A4 inducers or dabigatran.
- with congenital long QT syndrome.
- with a family history of sudden death or polymorphic ventricular arrythmia.
- with a QT/QTc interval > 500 msec, regardless of the correction method used.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Differentiation syndrome in patients with AML:**

TIBSOVO can cause a serious condition known as **differentiation syndrome** in patients with AML. Differentiation syndrome can be fatal if not treated, and symptoms may include non-infectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and creatinine increased. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. Patients must be informed of signs and symptoms of differentiation syndrome, be advised to contact their health professional immediately if these occur and the need to carry the Patient Alert Card with them at all times (see 7 WARNINGS AND PRECAUTIONS).

- **QTc interval prolongation:**

Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, dose reduce or interrupt, then resume dose or permanently discontinue TIBSOVO (see 4 DOSAGE AND ADMINISTRATION; 7 WARNINGS AND PRECAUTIONS; 8 ADVERSE REACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment should be initiated under the supervision of a health professional experienced in the use of anti-cancer medicinal products.

- Before taking TIBSOVO, patients must have confirmation of an IDH1 R132 mutation using an appropriate diagnostic test.

- An electrocardiogram (ECG) must be performed prior to treatment initiation. Heart rate corrected QT (QTc) should be less than 450 msec prior to treatment initiation and, in the presence of an abnormal QT, the benefit/risk of initiating TIBSOVO should be reassessed. In case QTc interval prolongation is between 480 msec and 500 msec, initiation of treatment with TIBSOVO should remain exceptional and be accompanied by close monitoring.

- An ECG must be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and then at least monthly for the duration of therapy. Any abnormalities should be managed promptly (see Table 1 and 7 WARNINGS AND PRECAUTIONS).

- If a moderate or strong CYP3A4 inhibitor cannot be avoided, the dose of TIBSOVO should be reduced to 250 mg once daily. If the moderate or strong inhibitor is discontinued, the dose of TIBSOVO should be increased (after at least 5 half-lives of the CYP3A4 inhibitor) to the recommended dose of 500 mg once daily (see 9 DRUG INTERACTIONS and 8 ADVERSE REACTIONS).

- Complete blood count and blood chemistries should be assessed prior to the initiation of TIBSOVO and for the duration of therapy as clinically indicated.

4.2 Recommended Dose and Dosage Adjustment

- ***Treatment of Acute myeloid leukemia***

The recommended dose is 500 mg TIBSOVO (2 x 250 mg tablets) taken orally once daily.

TIBSOVO should be started on Cycle 1 Day 1 and administered once daily during the 28-day cycle. It should be started in combination with azacitidine at 75 mg/m^2 of body surface area, intravenously or subcutaneously, once daily on Days 1-7 of each 28-day cycle. The first treatment cycle of azacitidine should be given at 100% of the dose. It is recommended that patients be treated for a minimum of 6 cycles.

For the posology and method of administration of azacitidine, please refer to the Product Monograph for azacitidine.

Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient (see 4 DOSAGE AND ADMINISTRATION (dose modification), 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS)

- ***Treatment of Cholangiocarcinoma***

The recommended dose is 500 mg TIBSOVO (2 x 250 mg tablets) taken orally once daily.

Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

Dose modifications for adverse reactions

Table 1 - Recommended Dose Modifications for Adverse Reactions

Adverse Reaction	Recommended Action
Differentiation syndrome (see 7 WARNINGS AND PRECAUTIONS, and 8 ADVERSE REACTIONS)	• If differentiation syndrome is suspected, administer systemic corticosteroids for a minimum of 3 days and taper only after symptom resolution. Premature discontinuation may result in symptom recurrence. • Initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days. • Interrupt TIBSOVO if severe signs/symptoms persist for more than 48 hours after initiation of systemic corticosteroids. • Resume treatment at 500 mg TIBSOVO once daily, when signs/symptoms are moderate or lower, and upon improvement in clinical condition.

Leukocytosis (white blood cell count > 25 x 10^9/L or an absolute increase in total white blood cell count > 15 x 10^9/L from baseline), (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS)	• Initiate treatment with hydroxyurea according to institutional standards of care and leukapheresis as clinically indicated. • Taper hydroxyurea only after leukocytosis improves or resolves. Premature discontinuation may result in recurrence. • Interrupt TIBSOVO if leukocytosis has not improved after initiation of hydroxyurea. • Resume treatment at 500 mg TIBSOVO once daily when leukocytosis has resolved.
QTc interval prolongation > 480 to 500 msec (Grade 2, see 7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS and 8 ADVERSE REACTIONS)	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medicinal products with known QTc interval-prolonging effects (see 9 DRUG INTERACTIONS). • Interrupt TIBSOVO until QTc interval returns to ≤ 480 msec. • Resume treatment at 500 mg TIBSOVO once daily after the QTc interval returns to ≤ 480 msec. • Monitor ECGs at least weekly for 2 weeks and as clinically indicated following return of QTc interval to ≤ 480 msec.
QTc interval prolongation > 500 msec (Grade 3, see 7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS and 8 ADVERSE REACTIONS)	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medicinal products with known QTc interval-prolonging effects (see 9 DRUG INTERACTIONS). • Interrupt TIBSOVO and monitor ECG every 24 h until QTc interval returns to within 30 msec of baseline or ≤ 480 msec. • In case of QTc interval prolongation > 550 msec, in addition to the interruption of TIBSOVO already scheduled, consider placing the patient under continuous electrocardiographic monitoring until QTc returns to values < 500 msec. • Resume treatment at 250 mg TIBSOVO once daily after QTc interval returns to within 30 msec of baseline or ≤ to 480 msec. • Monitor ECGs at least weekly for 2 weeks and as clinically indicated following return of QTc interval to within 30 msec of baseline or ≤ 480 msec. • If alternative etiology for QTc interval prolongation is identified, dose may be increased to 500 mg TIBSOVO once daily.

QTc interval prolongation with signs/symptoms of life-threatening ventricular arrhythmia (Grade 4, see 7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS and 8 ADVERSE REACTIONS)	• Permanently discontinue treatment.
Other Grade 3 or higher adverse reactions	• Interrupt TIBSOVO until toxicity resolves to Grade 1 or lower, or baseline, then resume at 500 mg daily (Grade 3 toxicity) or 250 mg daily (Grade 4 toxicity). • If Grade 3 toxicity recurs (a second time), reduce TIBSOVO dose to 250 mg daily until the toxicity resolves, then resume 500 mg daily. • If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue TIBSOVO.

Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Patients with Renal impairment

No dose adjustment is required in patients with mild (eGFR ≥ 60 to < 90 mL/min/1.73 m^2) or moderate (eGFR ≥ 30 to < 60 mL/min/1.73 m^2) renal impairment. A recommended dose has not been determined for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2).

TIBSOVO should be used with caution in patients with severe renal impairment and this patient population should be closely monitored (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Patients with Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Child Pugh class A). A recommended dose has not been determined for patients with moderate and severe hepatic impairment (Child Pugh classes B and C).

TIBSOVO should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Geriatrics (≥ 65 years of age)

No dose adjustment is required in elderly patients (≥ 65 years old, see 8 ADVERSE REACTIONS and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). No data are available for patients aged 85 years or older.

Pediatrics (< 18 years of age)

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

TIBSOVO should be taken orally once daily at about the same time each day. Patients should not eat anything for 2 hours before and through 1 hour after taking the tablets. (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

The tablets should be swallowed whole with water.

4.5 Missed Dose

If a dose of TIBSOVO is missed, the dose should be taken as soon as possible within 12 hours after the missed dose. Two doses of TIBSOVO should not be taken within 12 hours to make up for a missed dose. Return to normal dosing schedule the next day.

If a dose is vomited, replacement tablets should not be taken. The tablets should be taken as usual the following day.

5 OVERDOSAGE

In the event of overdose, toxicity is likely to manifest as exacerbation of the adverse reactions associated with TIBSOVO (see 8 ADVERSE REACTIONS). Patients should be closely monitored, including ECG monitoring, and provided with appropriate supportive care (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

There is no specific antidote for TIBSOVO overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet 250 mg	Colloidal silica (anhydrous), Croscarmellose sodium, Hypromellose, Hypromellose acetate succinate, Indigo carmine aluminum lake, Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Sodium lauryl sulfate, Titanium dioxide, Triacetin

TIBSOVO is a blue, oval shaped, film-coated tablet approximately 18 mm in length, debossed with "IVO" on one side and "250" on the other side.

TIBSOVO tablets are supplied in HDPE bottles with polypropylene (PP) child resistant closure and polyethylene (PE) faced induction heat seal liner containing 60 tablets each and a silica gel desiccant in a HDPE canister.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Differentiation syndrome in patients with Acute Myeloid Leukemia

Differentiation syndrome has been reported following treatment with TIBSOVO (see 8 ADVERSE REACTIONS). Differentiation syndrome may be life-threatening or fatal if not treated (see below and 4 DOSAGE AND ADMINISTRATION). Differentiation syndrome is associated with rapid proliferation and

differentiation of myeloid cells. Symptoms include non-infectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and creatinine increased. Patients must be informed of signs and symptoms of differentiation syndrome, be advised to contact their health professional immediately if these occur and the need to carry the Patient Alert Card with them at all times.

In study AG120-C-009, the median time to onset of differentiation syndrome was 20 days. Differentiation syndrome occurred as early as 3 days and up to 33 days after treatment initiation during combination therapy.

If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days.

If leukocytosis is observed, initiate treatment with hydroxyurea according to institutional standards of care and leukapheresis as clinically indicated (see 9 DRUG INTERACTIONS).

Taper corticosteroids and hydroxyurea only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. Interrupt treatment with TIBSOVO if severe signs/symptoms persist for more than 48 hours after the initiation of systemic corticosteroids and resume treatment at 500 mg TIBSOVO once daily when the signs/symptoms are moderate or lower and upon improvement in the patient's clinical condition (see 4 DOSAGE AND ADMINISTRATION).

Cardiovascular

QTc interval prolongation

QTc interval prolongation has been reported following treatment with TIBSOVO (see 8 ADVERSE REACTIONS). An ECG must be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains ≤ 480 msec (see 4 DOSAGE AND ADMINISTRATION). Any abnormalities should be managed promptly (see 4 DOSAGE AND ADMINISTRATION). In case of suggestive symptomatology, an ECG should be performed as clinically indicated. Conduct regular monitoring of electrolytes. In case of severe vomiting and/or diarrhea, an assessment of serum electrolytes abnormalities, especially hypokalemia and magnesium, must be performed.

QTc interval prolongation can lead to an increased risk of ventricular arrhythmias including torsades de pointes. Torsades de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsades de pointes increases with the magnitude of QTc prolongation produced by the drug. If sustained, torsades de pointes can progress to ventricular fibrillation and sudden cardiac death.

Risk factors for torsades de pointes in the general population include, but are not limited to, the following: female gender, age ≥65 years, baseline prolongation of the QTc interval, presence of genetic variants affecting cardiac ion channels or regulatory proteins (especially congenital long QT syndromes), family history of sudden cardiac death at <50 years of age, cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease), history of arrhythmias, electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia), conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating

disorders), bradycardia, acute neurological events (e.g., intracranial or subarachnoid hemorrhage, stroke, intracranial trauma), diabetes mellitus, and autonomic neuropathy.

Patients should be informed of the risk of QT prolongation, its signs and symptoms (palpitations, dizziness, syncope or even cardiac arrest) and be advised to contact their health professional immediately if these occur.

Concomitant administration of medicinal products known to prolong the QTc interval, and CYP3A4 inhibitors may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with TIBSOVO (see 4 DOSAGE AND ADMINISTRATION and 9 DRUG INTERACTIONS). Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. ECG should be performed prior to co-administration and then as clinically indicated. The dose of TIBSOVO should be reduced to 250 mg once daily if a moderate or strong CYP3A4 inhibitor cannot be avoided.

If administration of furosemide is clinically indicated to manage signs/symptoms of differentiation syndrome, patients should be closely monitored for electrolyte imbalances and QTc interval prolongation.

Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic monitoring of ECGs and electrolytes, during treatment with TIBSOVO.

Treatment with TIBSOVO should be permanently discontinued if patients develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia (see 4 DOSAGE AND ADMINISTRATION).

TIBSOVO should be used with caution in patients who either have low albumin levels or are underweight.

Dependence/Tolerance

Lactose intolerance

TIBSOVO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should avoid this medicinal product.

Driving and Operating Machinery

TIBSOVO has minor influence on the ability to drive and use machines. Fatigue and dizziness have been reported in some patients taking TIBSOVO (see 8 ADVERSE REACTIONS) and should be considered when assessing a patient's ability to drive or operate machines.

Hepatic/Biliary/Pancreatic

Patients with hepatic impairment

The safety and efficacy of TIBSOVO have not been established in patients with moderate and severe hepatic impairment (Child Pugh classes B and C). TIBSOVO should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Renal

Patients with severe renal impairment

The safety and efficacy of TIBSOVO have not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). TIBSOVO should be used with caution in patients with severe renal impairment and this patient population should be closely monitored (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Reproductive Health: Female and Male Potential

Women of childbearing potential should have a pregnancy test prior to starting treatment with TIBSOVO and should avoid becoming pregnant during therapy (see 7 WARNINGS AND PRECAUTIONS).

Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with TIBSOVO and for at least 1 month after the last dose.

TIBSOVO may decrease the systemic concentrations of hormonal contraceptives (such as norethisterone and ethinyl estradiol) and, therefore, concomitant use of an alternative contraceptive method such as barrier contraceptives is recommended (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Fertility

There are no human data on the effect of ivosidenib on fertility. No fertility studies in animals have been conducted to evaluate the effect of ivosidenib. Undesirable effects on reproductive organs were observed in a 28-day repeat dose toxicity study (see 16 NON-CLINICAL TOXICOLOGY). The clinical relevance of these effects is unknown.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate data on the use of ivosidenib in pregnant women. Studies in animals have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY).

TIBSOVO is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception. Patients should be informed of the potential risk to the fetus if it is used during pregnancy or if a patient (or female partner of a treated male patient) becomes pregnant during treatment or during the one-month period after the last dose.

7.1.2 Breast-feeding

It is unknown whether ivosidenib and its metabolites are excreted in human milk. No studies in animals have been conducted to evaluate the excretion of ivosidenib and its metabolites in milk. A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with TIBSOVO and for at least 1 month after the last dose.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not

authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in effectiveness or safety were observed between patients who were 65 years of age and older compared to younger patients. No dose adjustment is required in elderly patients (≥ 65 years old, see 8 ADVERSE REACTIONS and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). No data are available for patients aged 85 years or older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Newly diagnosed acute myeloid leukemia in combination with azacitidine

The safety of TIBSOVO in combination with azacitidine was evaluated in AML patients, in Study AG120-C-009. Patients received at least one dose of either TIBSOVO 500 mg daily or placebo. The median duration of treatment was 6 months (range 0 to 33 months) with TIBSOVO in combination with azacitidine.

The most common adverse reactions were vomiting (22%), neutropenia (19%), electrocardiogram QT prolonged (19%), differentiation syndrome (14%) and thrombocytopenia (14%).

The serious adverse reactions were differentiation syndrome (8%), neutropenia (1%) and thrombocytopenia (1%).

Fatal adverse events occurred in 15% of patients receiving TIBSOVO, including pneumonia and haemorrhage intracranial (3%) cases, and COVID-19, septic shock, ischaemic stroke, seizure, multiple organ dysfunction syndrome, adenocarcinoma and pulmonary embolism (1%). None were considered as treatment-related by the Investigator.

In patients treated with TIBSOVO in combination with azacitidine, the frequency of discontinuation of TIBSOVO due to adverse reactions was 6%. Adverse reactions leading to discontinuation were thrombocytopenia (3%), electrocardiogram QT prolonged and neutropenia (1%).

The frequency of dose interruption of TIBSOVO due to adverse reactions was 31%. The adverse reactions leading to dose interruption were neutropenia (19%), electrocardiogram QT prolonged (8%), thrombocytopenia (7%), leukopenia (3%) and differentiation syndrome (3%).

The frequency of dose reduction of TIBSOVO due to adverse reactions was 18%. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (10%), neutropenia (7%) and thrombocytopenia (1%).

Previously treated, locally advanced or metastatic cholangiocarcinoma

The safety of TIBSOVO was studied in patients with previously treated, locally advanced or metastatic cholangiocarcinoma in Study AG120-C-005. Patients received at least one dose of either TIBSOVO 500 mg daily or placebo. The median duration of treatment was 2.8 months (range 0.1 to 45.1 months) with TIBSOVO.

The most common adverse reactions were diarrhea (23%), nausea (23%) and fatigue (20%).

The serious adverse reactions were electrocardiogram QT prolonged, hyperbilirubinemia, and jaundice cholestatic (1%).

Fatal adverse events occurred in 5% of patients receiving TIBSOVO, including sepsis (2%) and pneumonia, intestinal obstruction, pulmonary embolism, and hepatic encephalopathy (1%). None were considered treatment-related by the Investigator.

In patients treated with TIBSOVO, the frequency of treatment discontinuation due to adverse reactions was 1%. Adverse reaction leading to discontinuation was hyperbilirubinemia (1%).

The frequency of dose interruption of TIBSOVO due to adverse reactions was 2%. The adverse reactions leading to dose interruption were fatigue (2%) and jaundice cholestatic (1%).

The frequency of dose reduction of TIBSOVO due to adverse reactions was 4%. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (3%) and neuropathy peripheral (1%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

AG120-C-009 Study (Newly diagnosed acute myeloid leukemia in combination with azacitidine)

In the randomized, placebo-controlled, phase 3 Study AG120-C-009, the safety profile of TIBSOVO was studied in patients with newly diagnosed AML. 72 patients were treated with TIBSOVO (500 mg daily) in combination with azacitidine, and 74 patients were given placebo in combination with azacitidine. The most common adverse reactions and laboratory abnormalities observed in Study AG120-C-009 are shown in Table 3.

Table 3 - Adverse Reactions in ≥5% Newly Diagnosed AML Patients Treated with TIBSOVO in Combination with azacitidine in Clinical Study AG120-C-009 (N=72)[1,2]

System Organ Class Preferred Term	TIBSOVO + azacitidine (N=72) n (%)	Placebo + azacitidine (Before crossover) (N=74) n (%)
Gastrointestinal disorders		
Vomiting	16 (22)	10 (14)
Blood and lymphatic system disorders		
Neutropenia	14 (19)	5 (7)
Thrombocytopenia	10 (14)	6 (8)
Differentiation syndrome	10 (14)	6 (8)
Leukocytosis	7 (10)	2 (3)
Leukopenia	4 (6)	1 (1)
Investigations		

Electrocardiogram QT prolonged	14 (19)	2 (3)
Nervous system disorders		
Headache	4 (6)	0
Psychiatric Disorder		
Insomnia	4 (6)	1 (1)

[1]*Data cut-off date 30 Jun 2022*
[2]*Adverse drug reactions related to AG120/placebo are included, regardless of relatedness with azacitidine. Relatedness was assessed by investigators.*
[3]*Grouped term includes vomiting and retching.*

AG120-C-005 Study (Previously treated, locally advanced or metastatic cholangiocarcinoma)

The safety of TIBSOVO was studied in patients with previously treated, locally advanced or metastatic cholangiocarcinoma in Study AG120-C-005 (see 14 CLINICAL TRIALS). Patients received at least one dose of either TIBSOVO 500 mg daily (N=123) or placebo (N=59). The most common adverse reactions and laboratory abnormalities observed in Study AG120-C-005 are shown in Table 4.

Table 4 - Adverse Reactions in ≥5% Patients with Locally Advanced or Metastatic Cholangiocarcinoma Treated with TIBSOVO in Clinical Study AG120-C-005 (N=123) [1,2]

System Organ Class Preferred Term	TIBSOVO (N=123) n (%)	Placebo (N=59) n (%)
Blood and lymphatic system disorders		
Anemia	6 (5)	0
Gastrointestinal disorders		
Nausea	28 (23)	9 (15)
Diarrhea	28 (23)	5 (8)
Abdominal pain[3]	12 (10)	3 (5)
Vomiting[4]	12 (10)	8(14)
General disorders and administration site conditions		
Fatigue[5]	24 (20)	7 (12)
Metabolism and nutrition disorders		
Decreased appetite	11 (9)	4 (7)
Investigations		
Aspartate aminotransferase increased	6 (5)	1 (2)
Electrocardiogram QT prolonged	8 (7)	1 (2)
Nervous system disorders		
Headache	10 (8)	1 (2)
Skin and subcutaneous tissue disorders		
Rash[6]	7 (6)	2 (3)

[1] *Final database lock date 21 Jun 2021*
[2] *Adverse drug reactions related to AG120/placebo are included. Relatedness was assessed by investigators.*

[3] Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, epigastric discomfort and abdominal tenderness (and gastrointestinal pain in the placebo group only).
[4] Grouped term includes vomiting and retching.
[5] Grouped term includes asthenia and fatigue.
[6] Grouped term includes rash, rash maculo-papular, erythema, rash macular, dermatitis exfoliative generalized, drug eruption, and drug hypersensitivity.

8.3 Less Common Clinical Trial Adverse Reactions

Newly diagnosed acute myeloid leukemia in combination with azacitidine

Other adverse reactions (all Grades) reported in < 5% of patients treated with TIBSOVO + azacitidine in newly diagnosed AML

Nervous system disorders: Dizziness (4%), Neuropathy peripheral (4% - grouped term includes neuropathy peripheral, peripheral sensory neuropathy, and paraesthesia)

Previously treated, locally advanced or metastatic cholangiocarcinoma

Other adverse reactions (all Grades) reported in < 5% of patients treated with TIBSOVO in cholangiocarcinoma

Gastrointestinal disorders: Ascites (1%)
Hepatobiliary disorders: Jaundice cholestatic (1%), Hyperbilirubinemia (1%)
Investigations: Blood bilirubin increased (3%), Alanine aminotransferase increased (2%), White blood cell count decreased (3%), Platelet count decreased (1%)
Nervous system disorders: Neuropathy peripheral (4% - grouped term includes neuropathy peripheral, peripheral sensory neuropathy, and paraesthesia)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Newly diagnosed acute myeloid leukemia in combination with azacitidine

Table 5 - Select Laboratory Abnormalities[1, 2] (≥10%) That Worsened from Baseline in Patients with AML Who Received TIBSOVO + azacitidine for Hematology Parameters in AG120-C-009 study

	TIBSOVO + azacitidine		Placebo + azacitidine	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Leukocytes decreased	46 (64)	41 (57)	48 (65)	44 (59)
Platelets decreased	43 (60)	34 (47)	53 (72)	42 (57)
Hemoglobin decreased	41 (57)	34 (47)	52 (70)	44 (59)
Neutrophils decreased	19 (26)	18 (25)	25 (34)	23 (32)
Lymphocytes increased	18(25)	1 (1)	8 (11)	1 (1)
Lymphocytes decreased	41 (57)	23 (32)	50 (68)	28 (38)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

[2] *The denominator used to calculate percentages is the number of treated subjects who can be evaluated for CTCAE criteria for each parameter in each arm.*

Table 6 - Select Laboratory Abnormalities[1, 2] (≥10%) That Worsened from Baseline in Patients with AML Who Received TIBSOVO + azacitidine for Chemistry Parameters in AG120-C-009 study

	TIBSOVO + azacitidine		Placebo + azacitidine	
Parameter	**All Grades n n (%)**	**Grade ≥ 3 n (%)**	**All Grades n n (%)**	**Grade ≥ 3 n (%)**
Albumin decrease	31 (43)	3 (4)	44 (59)	5 (7)
Bicarbonate decrease	21 (30)	1 (1)	20 (27)	0
Bilirubin increase	16 (22)	4 (6)	16 (22)	1 (1)
Glucose increased	41 (57)	9 (13)	35 (47)	8 (11)
Phosphate decreased	29 (40)	7 (10)	27 (36)	9 (12)
Aspartate Aminotransferase increased	26 (36)	0	18 (24)	0
Alanine Aminotransferase increase	14 (19)	0	24 (32)	0
Magnesium decreased	29 (40)	1 (1)	22 (30)	0
Magnesium increase	8 (11)	0	9 (12)	1 (1)
Calcium increase	14 (19)	2 (3)	5 (7)	2 (3)
Calcium decrease	29 (40)	4 (6)	32 (43)	4 (5)
Alkaline Phosphatase increased	24 (33)	0	24 (32)	1 (1)
Potassium increased	22 (31)	4 (6)	10 (14)	1 (1)
Potassium decrease	23 (32)	4 (6)	32 (43)	12 (16)
Creatinine increase	25 (35)	2 (3)	31 (42)	1 (1)
Sodium decrease	32 (44)	11 (15)	34 (46)	13 (18)

[1] *Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.*

[2] *The denominator used to calculate percentages is the number of treated subjects who can be evaluated for CTCAE criteria for each parameter in each arm.*

Of the 72 patients with newly diagnosed AML who were treated with TIBSOVO in combination with azacitidine in study AG120-C-009, electrocardiogram QT prolonged was reported and assessed as related to TIBSOVO in 19% of patients. Ten percent (10%) of patients experienced Grade 3 or higher reactions. Based on ECG analysis, 17% of patients treated with TIBSOVO in combination with azacitidine, who had at least one post-baseline ECG assessment, were found to have a QTc interval > 500 msec, 26% had an increase from baseline QTc > 60 msec (Table 7). One percent (1%) of patients discontinued TIBSOVO treatment due to electrocardiogram QT prolonged, dose interruption and reduction were required in 8% and 10% of patients, respectively. The median time to onset of QT prolongation assessed as related to TIBSOVO in patients treated with TIBSOVO was 31 days. Electrocardiogram QT prolonged occurred as early as 4 days and up to 27 months after treatment initiation.

Table 7 - Summary of Notable ECG Values During the On-treatment Period (AG120-C-009 Safety Analysis Set)

ECG Parameter Criteria	TIBSOVO + azacitidine n (%)	Placebo + azacitidine n (%)

QTcF (msec)		
>30 increase from baseline	46 (66)	28 (39)
>60 increase from baseline	18 (26)	10 (14)
>450	45 (63)	25 (35)
>480	19 (26)	6 (8)
>500	12 (17)	2 (3)

Abbreviations: ECG = electrocardiogram; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Previously treated, locally advanced or metastatic cholangiocarcinoma

Table 8 - Selected Laboratory Abnormalities Occurring in ≥ 10% of Patients Receiving TIBSOVO for Hematology Parameters in AG120-C-005[1] study

	TIBSOVO		Placebo	
Parameter	**All Grades n (%)**	**Grade > 3 n (%)**	**All Grades n (%)**	**Grade > 3 n (%)**
Hemoglobin decreased	48 (40)	9 (8)	14 (25)	0

[1] *Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.*

Table 9 - Selected Laboratory Abnormalities Occurring in ≥ 10% of Patients Receiving TIBSOVO for Chemistry Parameters in AG120-C-005[1] study

	TIBSOVO		Placebo	
Parameter	**All Grades n (%)**	**Grade > 3 n (%)**	**All Grades n (%)**	**Grade > 3 n (%)**
AST increased	41 (34)	5 (4)	14 (24)	1 (2)
Bilirubin increased	36 (30)	15 (13)	11 (19)	2 (3)

[1] *Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.*

Of the 123 patients with locally advanced or metastatic cholangiocarcinoma treated with TIBSOVO monotherapy in study AG120-C-005, electrocardiogram QT prolonged was reported and assessed as related to TIBSOVO in 7% of patients. Based on ECG analysis, 2% of patients had a QTc interval > 500 msec and 5% had QTc interval prolongation > 60 msec from baseline (Table 10). Dose reduction to manage signs/symptoms was required in 3% of patients. The median time to onset of QT prolongation assessed as related to TIBSOVO in patients treated with TIBSOVO monotherapy was 30 days. Electrocardiogram QT prolonged occurred as early as 1 day and up to 23 months after treatment initiation.

Table 10 - Summary of Notable ECG values During the On-treatment Period – Cholangiocarcinoma Population (Safety Analysis Set)

ECG Parameter Criteria	**TIBSOVO n (%)**	**Placebo n (%)**
QTcF (msec)		

>30 increase from baseline	53 (43)	10 (17)
>60 increase from baseline	6 (5)	0
>450	53 (43)	11 (19)
>480	8 (7)	0
>500	3 (2)	0

Abbreviations: ECG = electrocardiogram; QTcF = QT interval corrected for heart rate using Fridericia's formula.

8.5 Post-Market Adverse Reactions

No new safety information has been identified through post-marketing use.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

TIBSOVO has minor influence on the ability to drive and use machines (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 11 - Established or Potential Drug-Drug Interactions

Proper name	Source of Evidence	Effect	Clinical comment
Strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort (Hypericum perforatum))	T	Expected to decrease plasma concentrations of ivosidenib.	Concomitant administration of strong CYP3A4 inducers is expected to decrease plasma concentrations of TIBSOVO. Co-administration of strong CYP3A4 inducers with TIBSOVO is contraindicated (see 2 CONTRAINDICATIONS). Clinical studies evaluating the pharmacokinetics of TIBSOVO in the presence of a CYP3A4 inducer have not been conducted.

Proper name	Source of Evidence	Effect	Clinical comment
Moderate CYP3A4 inhibitors (aprepitant, ciclosporin, diltiazem, erythromycin, fluconazole, grapefruit and grapefruit juice, isavuconazole, verapamil) **Strong CYP3A4 inhibitors** (clarithromycin, itraconazole, ketoconazole, posaconazole, ritonavir, voriconazole)	CT; T	Increases plasma concentrations of ivosidenib. In healthy subjects, administration of a single dose of 250 mg ivosidenib and 200 mg itraconazole once daily for 18 days increased the ivosidenib AUC by 169% (90% CI: 145, 195) with no change in C_{max}.	This may increase the risk of QTc interval prolongation and suitable alternatives that are not moderate or strong CYP3A4 inhibitors should be considered whenever possible during treatment with TIBSOVO. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. If use of moderate or strong CYP3A4 inhibitors cannot be avoided, the recommended dose of TIBSOVO should be reduced to 250 mg once daily (see 4 DOSAGE AND ADMINISTRATION and 7 WARNING AND PRECAUTIONS).
Medicinal products known to prolong the QTc interval (e.g. anti-arrhythmics, fluoroquinolones, 5 HT3 receptor antagonists, triazole antifungals)	T		Concomitant administration of medicinal products known to prolong the QTc interval may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with TIBSOVO. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible (see 4 DOSAGE AND ADMINISTRATION and 7 WARNING AND PRECAUTIONS).
Interactions with transporters	T	Ivosidenib is a substrate for P-glycoprotein (P-gp) and has potential to induce P-gp. Ivosidenib is not a substrate for BCRP or hepatic transporters	There is potential for TIBSOVO to alter the systemic exposure to active substances that are predominantly transported by P-gp (e.g., dabigatran). Concomitant administration of dabigatran is contraindicated with TIBSOVO.

Proper name	Source of Evidence	Effect	Clinical comment
		OATP1B1 and OATP1B3. Ivosidenib does not inhibit BCRP, OAT1, and OCT2. ivosidenib is an inhibitor of OAT3, OATP1B1, OATP1B3 and P-gp.	TIBSOVO may increase systemic exposure to OAT3 or OATP1B1 and OATP1B3 substrates. Concomitant administration of OAT3 substrates (e.g. benzylpenicillin, furosemide) or sensitive OATP1B1 and OATP1B3 substrates (e.g. atorvastatin, pravastatin, rosuvastatin) should be avoided whenever possible during treatment with TIBSOVO. Patients should be treated with caution if use of a suitable alternative is not possible. If administration of furosemide is clinically indicated to manage signs/symptoms of differentiation syndrome, patients should be closely monitored for electrolyte imbalances and QTc interval prolongation.
Cytochrome P450 (CYP) enzyme substrates • **CYP3A4 substrates with a narrow therapeutic index** (alfentanil, ciclosporin, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) • **CYP2B6 substrates with a narrow therapeutic index** (cyclophosphamide, ifosfamide, methadone) • **CYP2C8 substrates with a narrow therapeutic index** (paclitaxel, pioglitazone, repaglinide)	T	Ivosidenib induces CYP3A4, CYP2B6, CYP2C8, CYP2C9 and may induce CYP2C19. Co-administration will decrease systemic exposure to substrates of these enzymes.	Use alternative therapies that are not sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9 or CYP2C19 during TIBSOVO treatment. If co-administration of TIBSOVO with sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9 or CYP2C19 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs. (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). Do not administer TIBSOVO with anti-fungal agents that are substrates of CYP3A4 due to

Proper name	Source of Evidence	Effect	Clinical comment
• **CYP2C9 substrates with a narrow therapeutic index** (phenytoin, warfarin) • **CYP2C19 substrates** (omeprazole)			expected loss of antifungal efficacy. TIBSOVO may decrease the systemic concentrations of hormonal contraceptives that are substrates of CYP3A4 (such as norethisterone and ethinyl estradiol) and, therefore, concomitant use of a barrier method of contraception is recommended for at least 1 month after the last dose (see 7 WARNING AND PRECAUTIONS, 7.1 Special Populations).
Uridine diphosphate glucuronosyltransferases (UGTs) substrates (e.g. lamotrigine, raltegravir)	T	Ivosidenib has the potential to induce UGTs and decrease systemic exposure of substrates of UGT enzymes.	Suitable alternatives that are not UGT substrates should be considered during treatment with TIBSOVO. Patients should be monitored for loss of UGT substrate efficacy if use of such medicinal products cannot be avoided.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drugs that Affect Electrolytes

TIBSOVO should be used with caution with drugs that can decrease electrolyte levels and possibly increase the risk of QTc interval prolongation. Electrolyte levels should be monitored and maintained within the normal range to mitigate this risk.

Drugs that Reduce Heart Rate

Bradycardia can increase the risk of QTc prolongation and torsades de pointes. TIBSOVO should be used with caution if used concomitantly with drugs that reduce the heart rate. The heart rate should be monitored and maintained within the normal range.

9.5 Drug-Food Interactions

A drug-food interaction study demonstrated that administration of TIBSOVO 500 mg with a high-fat, high-calorie meal increased C_{max} and AUC_T by approximately 98% and 26%, respectively, but did not have a significant effect on T_{max}, relative to administration of TIBSOVO under fasting conditions.

Grapefruit and grapefruit juice may increase plasma concentrations of TIBSOVO.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort herb may interact with TIBSOVO.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ivosidenib is an inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumorigenesis in both hematologic and non-hematologic malignancies. The mechanism of action of ivosidenib beyond its ability to reduce 2-HG and restore cellular differentiation is not fully understood across indications.

10.2 Pharmacodynamics

Multiple doses of ivosidenib 500 mg daily decreased plasma concentrations of 2-HG in patients with hematological malignancies and cholangiocarcinoma with mutated IDH1 to levels approximating those observed in healthy subjects. In bone marrow of patients with hematological malignancies and in tumor biopsy of patients with cholangiocarcinoma, the mean (% coefficient of variation [%CV]) reduction in 2-HG concentrations were 93.1% (11.1%) and 82.2% (32.4%), respectively.

Using an ivosidenib concentration-QTc model constructed using triplicate ECG data from 136 patients with R/R AML, a concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) was predicted at the steady-state C_{max} based on an analysis of 173 patients with advanced hematological malignancies, primarily R/R AML, who received 500 mg ivosidenib once daily. From a concentration-QTc model generated using triplicate ECG data from 101 patients with solid tumors (45.5% cholangiocarcinoma), a concentration-dependent prolongation of approximately 17.2 msec (90% CI: 14.3, 20.2) was predicted at the steady-state C_{max} following a 500 mg daily dose using data from 166 patients with cholangiocarcinoma pooled from a phase 1 and phase 3 study (7 WARNINGS AND PRECAUTIONS, 7.1 Special populations and 9 DRUG INTERACTIONS).

10.3 Pharmacokinetics

Table 12 - Summary of ivosidenib Steady-State Pharmacokinetic Parameters in Cholangiocarcinoma (CCA) and AML patients treated with TIBSOVO

	C_{max}	T_{max}[a]	$t_{½}$ (h)	AUC	CL/F	Vc/F
Mean (CV%) in CCA	4,799 ng/mL (33%)	2 hr	129 hr (102%)	86,382 (34%)	6.1 L/hour (31%)	3.20 L/kg (47.8%)
Mean (CV%) in AML	6,145 ng/mL (34%)	2 hr	98 hr (42%)	106,326 (41%)	4.6 L/hour (35%)	2.97 L/kg (25.9%)

[a] *T_{max} expressed as median*

A total of 10 clinical studies have contributed to the characterisation of the clinical pharmacology of ivosidenib. Five studies have been conducted in healthy subjects and 3 studies have been conducted in patients with advanced malignancies including 2 studies in patients with cholangiocarcinoma. Two studies have been conducted in patients with newly diagnosed AML receiving ivosidenib in combination with azacitidine. Pharmacokinetic endpoints have been assessed in plasma and urine. Pharmacodynamic endpoints have been assessed in plasma, urine, tumor biopsy, and bone marrow (for studies in patients with advanced malignancies only).
The steady-state pharmacokinetics of ivosidenib 500 mg were comparable between patients with newly diagnosed AML and cholangiocarcinoma.

Absorption
After a single 500 mg oral dose, the median time to C_{max} (T_{max}) was approximately 2 hours in newly diagnosed AML patients treated with a combination of ivosidenib and azacitidine and in cholangiocarcinoma patients.

In patients with newly diagnosed AML treated with a combination of ivosidenib (500 mg daily dose) and azacitidine, the mean steady-state C_{max} was 6,145 ng/mL (CV%: 34) and the mean steady-state AUC was 106,326 ng hr/mL (CV%: 41).

In patients with cholangiocarcinoma, the mean C_{max} was 4,060 ng/mL (%CV: 45) after a single dose of 500 mg and 4,799 ng/mL (CV%: 33) at steady state for 500 mg daily. The AUC was 86,382 ng·hr/mL (CV%: 34).

Accumulation ratios were approximately 1.6 for AUC and 1.2 for C_{max} in patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine and approximately 1.5 for AUC and 1.2 for C_{max} in patients with cholangiocarcinoma, over one month, when ivosidenib was administered at 500 mg daily. Steady-state plasma levels were reached within 14 days of once daily dosing.
Significant increases in ivosidenib C_{max} (by approximately 98%) and AUC_T (by approximately 26%) were observed following administration of a single dose of 500 mg ivosidenib tablets with a high-fat meal (approximately 900 to 1,000 calories, 56% to 60% fat) in healthy subjects (see 9 DRUG INTERACTIONS, 9.5 Drug-Food interactions, 4 DOSAGE AND ADMINISTRATION).

Distribution
Based on a population pharmacokinetic analysis the mean apparent volume of distribution of ivosidenib at steady-state (Vc/F) is 3.20 L/kg (CV%: 47.8) in patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine and 2.97 L/kg (CV%: 25.9) in patients with cholangiocarcinoma treated with ivosidenib monotherapy.

Metabolism
Ivosidenib was the predominant component (> 92%) of total radioactivity in plasma from healthy subjects. It is primarily metabolised by oxidative pathways mediated largely by CYP3A4 with minor contributions by N dealkylation and hydrolytic pathways.

Ivosidenib induces CYP3A4 (including its own metabolism), and CYP2B6, CYP2C8, CYP2C9, and may induce CYP2C19 and UGTs. Therefore, it may decrease systemic exposure of substrates of these enzymes (see 9 DRUG INTERACTIONS and 7 WARNING AND PRECAUTIONS, 7.1 Special Populations).

Ivosidenib is a substrate for P-glycoprotein (P-gp) and has the potential to induce P-gp. Ivosidenib is not

a substrate for BCRP or hepatic transporters OATP1B1 and OATP1B3 (see 4 DOSAGE AND ADMINISTRATION).

Ivosidenib is an inhibitor of OAT3, OATP1B1, OATP1B3 and P-gp. Ivosidenib does not inhibit BCRP, OAT1, and OCT2 (see 9 DRUG INTERACTIONS).

Elimination
In patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine, the mean apparent clearance of ivosidenib at steady state was 4.6 L/hour (35%) with a mean terminal half-life of 98 hours (42%).

In patients with cholangiocarcinoma, the mean apparent clearance of ivosidenib at steady state was 6.1 L/hour (31%) with a mean terminal half-life of 129 hours (102%).

In healthy subjects, 77% of a single ivosidenib oral dose was found in the faeces of which 67% was recovered unchanged. Approximately 17% of a single oral dose was found in the urine of which 10% was recovered unchanged.

Linearity/non-linearity
The AUC and C_{max} of ivosidenib increased in a less than dose proportional manner from 200 mg to 1,200 mg once daily (0.4 to 2.4 times the recommended dose).

Special Populations and Conditions

- **Geriatrics:** No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in older patients up to 84 years. The pharmacokinetics of ivosidenib in patients 85 years of age or older is unknown (see 4 DOSAGE AND ADMINISTRATION).
- **Hepatic Insufficiency:** Using the NCI classification, no clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in patients with mild hepatic impairment. The pharmacokinetics of ivosidenib in patients with moderate and severe hepatic impairment are unknown in patients with newly diagnosed AML and with cholangiocarcinoma. No PK data in patients with hepatic impairment stratified by the Child-Pugh classification are available (see 4 DOSAGE AND ADMINISTRATION).
- **Renal Insufficiency:** No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2). The pharmacokinetics of ivosidenib in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or renal impairment requiring dialysis are unknown (see 4 DOSAGE AND ADMINISTRATION).
- **Other:** No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed based on gender, race, body weight or ECOG performance status.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C - 30°C. Keep the bottle tightly closed in order to protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS
No special requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

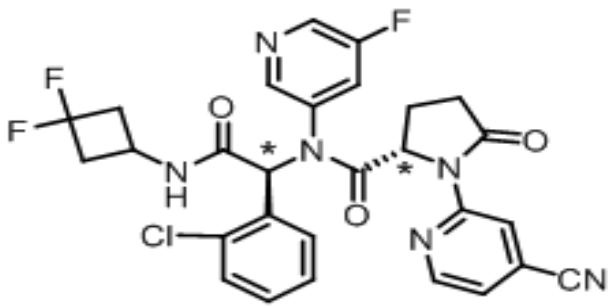
Drug Substance

Proper / Common name: ivosidenib

Chemical name: Glycinamide, 1-(4-cyano-2-pyridinyl)-5-oxo-L-prolyl-2-(2-chlorophenyl)-N- (3,3-difluorocyclobutyl)-N2-(5-fluoro-3-pyridinyl)-, (2S)-

Molecular formula and molecular mass: $C_{28}H_{22}ClF_3N_6O_3$, 583.0 g/mol

Structural formula:



∗ denotes stereocenter

Physicochemical properties: It is a white to light yellow crystalline solid. Ivosidenib is practically insoluble in aqueous solutions between pH 1.2 and 7.4.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Newly diagnosed acute myeloid leukemia in combination with azacitidine

The efficacy and safety of TIBSOVO was evaluated in a randomized, multicenter, double-blind, placebo-controlled clinical study (AG120-C-009) of 146 adult patients with previously untreated AML with an IDH1 mutation who were ineligible for intensive induction chemotherapy, based on at least one of the following criteria: 75 years or older, Eastern Cooperative Oncology Group (ECOG) performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, creatinine clearance < 45 mL/min, or other comorbidity. Gene mutation analysis for central confirmation of IDH1 mutation from bone marrow and/or peripheral blood were conducted for all subjects. Patients were randomized to receive either TIBSOVO 500 mg or matched placebo orally once daily with azacitidine 75 mg/m^2/day subcutaneously or intravenously for 1 week every 4 weeks until the end of the study, disease progression or unacceptable toxicity.

Table 13 - Summary of Patient Demographics and Disease Characteristics for Clinical Trials in Newly Diagnosed AML in Combination with azacitidine

	TIBSOVO + azacitidine N=72	Placebo + azacitidine N=74
Demographics		
Age (Years) Median (Min, Max)	76 (58, 84)	76 (45, 94)
Age Categories, n (%)		
< 65 years	4 (6)	4 (5)
65 years to < 75 years	29 (40)	27 (36)
≥ 75 years	39 (54)	43 (58)
Sex, n (%)		
Male	42 (58)	38 (51)
Female	30 (42)	36 (49)
Race, n (%)		
Asian	15 (21)	19 (26)
White	12 (17)	12 (16)
Black or African American	0	2 (3)
Other	1 (1)	1 (1)
Not provided	44 (61)	40 (54)
Disease Characteristics		
ECOG PS, n (%)		
0	14 (19)	10 (14)
1	32 (44)	40 (54)
2	26 (36)	24 (32)
IDH1 Mutation, n (%)[1]		
R132C	45 (63)	51 (69)
R132H	14 (19)	12 (16)
R132G	6 (8)	4 (5)
R132L	3 (4)	0
R132S	2 (3)	6 (8)
Wild type	1 (1)	0
Missing	1 (1)	1 (1)
Cytogenetic risk status[2] n (%)		
Favorable	3 (4)	7 (9)
Intermediate	48 (67)	44 (59)
Poor	16 (22)	20 (27)
Other	3 (4)	1 (1)
Missing	2 (3)	2 (3)
Transfusion Dependent at Baseline[3], n (%)	39 (54)	40 (54)
Type of AML, n (%)		
De novo AML	54 (75)	53 (72)
Secondary AML	18 (25)	21 (28)
Therapy-related AML	2 (3)	1 (1)
MDS related	10 (14)	12 (16)
MPN related	4 (6)	8 (11)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; MPN = Myeloproliferative Neoplasm; MDS = Myelodysplastic syndrome
[1] Using confirmatory Abbott RealTime IDH1 assay testing results.
[2] Cytogenetic risk status: National Comprehensive Cancer Network (NCCN) guidelines.
[3] Patients were defined as transfusion dependent at baseline if they received any red blood cell or platelet transfusion within 56 days prior to the first dose of TIBSOVO.

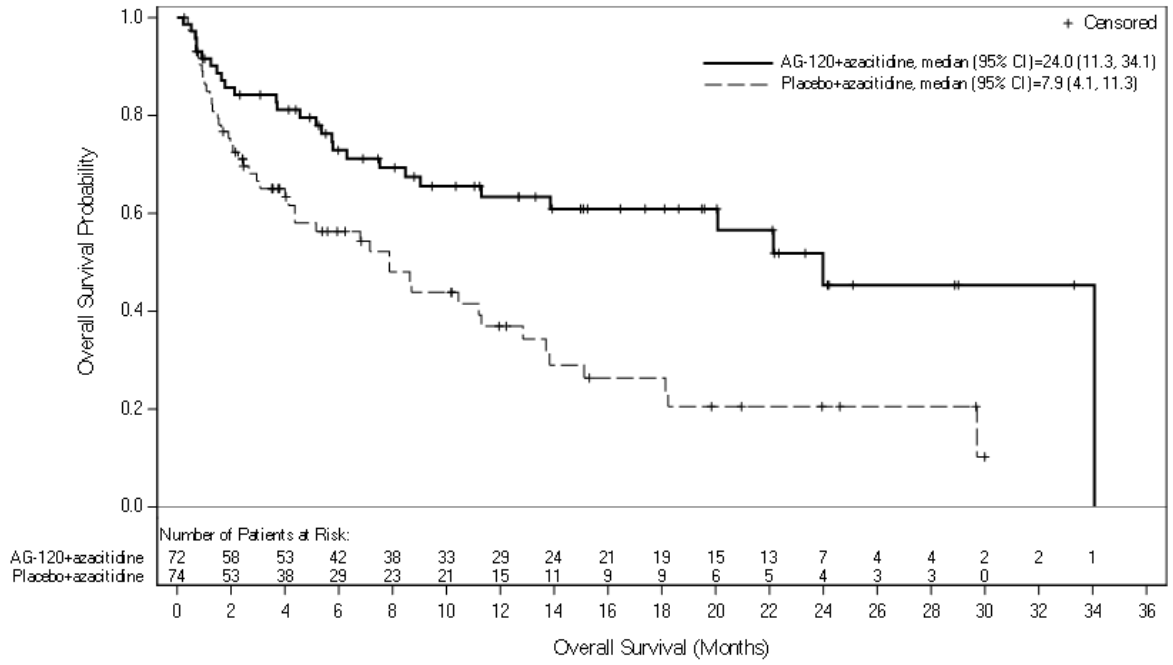
Efficacy was based on the primary efficacy endpoint event-free survival (EFS), measured from the date of randomization until treatment failure, relapse from remission, or death by any cause. Treatment failure was defined as failure to achieve complete remission (CR) by week 24. Overall Survival (OS), CR rate, CR + CR with partial hematologic recovery (CR + CRh) rate and objective response rate (ORR) were key secondary efficacy endpoints (Table 14 and Figure 1).

Table 14 - Efficacy Results in Patients with Newly Diagnosed AML in combination with azacitidine

Endpoint	TIBSOVO (500 mg daily) + azacitidine N=72	Placebo + azacitidine N=74
Event-Free Survival, events (%)	46 (63.9)	62 (83.8)
Treatment Failure	42 (58.3)	59 (79.7)
Relapse	3 (4.2)	2 (2.7)
Death	1 (1.4)	1 (1.4)
Hazard ratio[1] (95% CI)	0.33 (0.16, 0.69)	
OS events (%)	28 (38.9)	46 (62.2)
Median OS (95% CI) months	24.0 (11.3, 34.1)	7.9 (4.1, 11.3)
Hazard ratio[1] (95% CI)	0.44 (0.27, 0.73)	
CR, n (%)	34 (47.2)	11 (14.9)
95% CI[2]	(35.3, 59.3)	(7.7, 25.0)
Odds Ratio[3] (95% CI)	4.76 (2.15, 10.50)	
CR + CRh rate, n (%)	38 (52.8)	13 (17.6)
95% CI[2]	(40.7, 64.7)	(9.7, 28.2)
Odds Ratio[3] (95% CI)	5.01 (2.32, 10.81)	
CR + CRi rate, n (%)	39 (54.2)	12 (16.2)
95% CI[2]	(42.0, 66.0)	(8.7, 26.6)
Odds Ratio[3](95% CI)	5.90 (2.69, 12.97)	

CI: confidence interval; CR = Complete remission; CRh = Complete remission with partial hematologic recovery; CRi = Complete remission with incomplete hematologic recovery; OS = Overall survival;
[1] Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomization stratification factors (AML status and geographic region) with PBO+AZA as the denominator. (AML status and geographic region). 1-sided p-value < 0.0017 was required to achieve statistical significance.
[2] CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.
[3] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with PBO+AZA as the denominator.

Figure 1: Kaplan Meier Plot of Overall Survival (OS)



AG120=ivosidenib

An updated OS analysis, carried out at 64.2% (N = 95) of events, confirmed the overall survival benefit of TIBSOVO in combination with azacitidine compared to placebo in combination with azacitidine with a median OS of 29.3 months vs 7.9 months, respectively (HR = 0.42; 95% CI: 0.27 to 0.65).

Previously treated, locally advanced or metastatic cholangiocarcinoma

The efficacy of TIBSOVO was evaluated in a randomized (2:1), multicenter, double-blind, placebo-controlled, phase 3 clinical trial (Study AG120-C-005) of 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation whose disease had progressed following at least 1 but not more than 2 prior treatment regimens including at least one gemcitabine- or 5-FU-containing regimen and an expected survival of ≥ 3 months.

Patients were randomized to receive either TIBSOVO 500 mg orally once daily or matched placebo until disease progression or development of unacceptable toxicity. Randomization was stratified by number of prior therapies (1 or 2). Eligible patients who were randomized to placebo were allowed to cross over to receive TIBSOVO after documented radiographic disease progression as assessed by the investigator.

Table 15 - Summary of Patient Demographics and Disease Characteristics for Clinical Trials in Previously Treated, Locally Advanced or Metastatic Cholangiocarcinoma

	Placebo (N=61)	TIBSOVO (N=124)
Demographic		
Age (Years) Median (Min, Max)	63.0 (40, 83)	61 (33, 80)
Age Category (years), n (%)		

<45	3 (5)	11 (9)
45 - <65	33 (54)	67 (54)
≥65	25 (41)	46 (37)
Sex, n (%)		
Male	24 (39)	44 (36)
Female	37 (61)	80 (65)
Race, n (%)		
Asian	8 (13)	15 (12)
White	35 (57)	70 (57)
Other	1 (2)	4 (3)
Missing	17 (28)	35 (28)
Disease Characteristics		
ECOG at Baseline n (%)		
0	19 (31)	49 (40)
1-3	42 (69)	75 (60)
IDH1 Mutation[1] n (%)		
R132C	45 (74)	84 (68)
R132G	6 (10)	17 (14)
R132H	2 (3)	0
R132L	7 (12)	21 (17)
R132S	1 (2)	2 (2)
Cholangiocarcinoma Type at Diagnosis n (%)		
Intrahepatic	58 (95)	111 (90)
Extrahepatic and Perihilar	1 (2)	5 (4)
Unknown	2 (3)	8 (7)
Randomization Strata n (%)		
1 Prior Line of Therapy	33 (54)	66 (53)
2 Prior Lines of Therapy	28 (46)	58 (47)
Extent of Disease at Screening n (%)		
Local/Regional	5 (8)	9 (7)
Metastatic[2]	56 (92)	115 (93)
Biliary Stent at Screening n (%)		
Yes	7 (11)	14 (11)
No	54 (89)	110 (89)
Had Ascites at Screening n (%)		
Yes	13 (21)	34 (27)
No	48 (79)	90 (73)

Abbreviations : Max = maximum ; Min = minimum. Abbreviations: ECOG = Eastern Cooperative Oncology Group; IDH = isocitrate dehydrogenase.

[1]From IDH1 central testing.

[2]Subject with both local/regional and metastatic disease is considered as metastatic.

The primary efficacy outcome measure was Progression Free Survival (PFS) as determined by Independent Radiology Center (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, which was defined as time from randomization to disease progression or death due to any cause.

Overall Survival (OS) was a secondary efficacy endpoint. As allowed per protocol, a large proportion (70.5%) of patients in the placebo arm crossed over to receive TIBSOVO following radiographic disease progression as assessed by the Investigator.

Efficacy results are summarised in Table 16.

Table 16 - Efficacy Results in Patients with Locally Advanced or Metastatic Cholangiocarcinoma

Endpoint	**TIBSOVO (500 mg daily)**	**Placebo**
Progression-Free Survival (PFS) by IRC Assessment	**N=124**	**N=61**
Events, n (%)	76 (61)	50 (82)
Progressive Disease	64 (52)	44 (72)
Death	12 (10)	6 (10)
Median PFS, months (95% CI)	2.7 (1.6, 4.2)	1.4 (1.4, 1.6)
Hazard ratio (95% CI)[1]	0.37 (0.25, 0.54)	
P-value[2]	<0.0001	
PFS Rate (%)[3]		
6 months	32.0	NE
12 months	21.9	NE
Overall Survival[4]	**N=126**	**N=61**
Deaths, n (%)	100 (79)	50 (82)
Median OS (months, 95% CI)	10.3 (7.8, 12.4)	7.5 (4.8, 11.1)
Hazard ratio (95% CI)[1]	0.79 (0.56, 1.12)	
P-value[2]	0.093	

IRC: Independent Radiology Center; CI: Confidence Interval; NE = not estimable.

[1] Hazard ratio is calculated from stratified Cox regression model. Stratification factor is the number of prior line of therapies at randomization.

[2] P-value is calculated from the one-sided stratified log-rank test without adjusting for crossover. Stratification factor is the number of prior line of therapies at randomization.

[3] Based on Kaplan-Meier estimation. No patients randomized to placebo achieved PFS of 6 months or longer.

[4] OS results are based on the final analysis of OS (based on 150 deaths; data cut off: 31 May 2020) which occurred 16 months after the final analysis of PFS (data cut off: 31 January 2019).

Figure 2: Kaplan Meier Plot of Progression-Free Survival per IRC

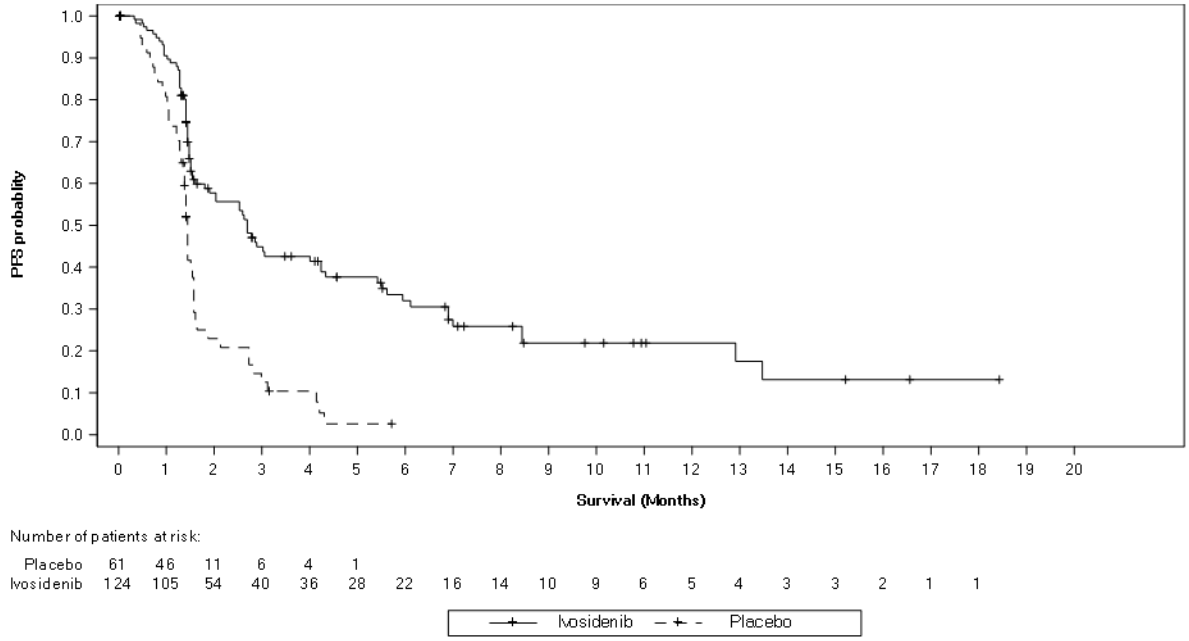
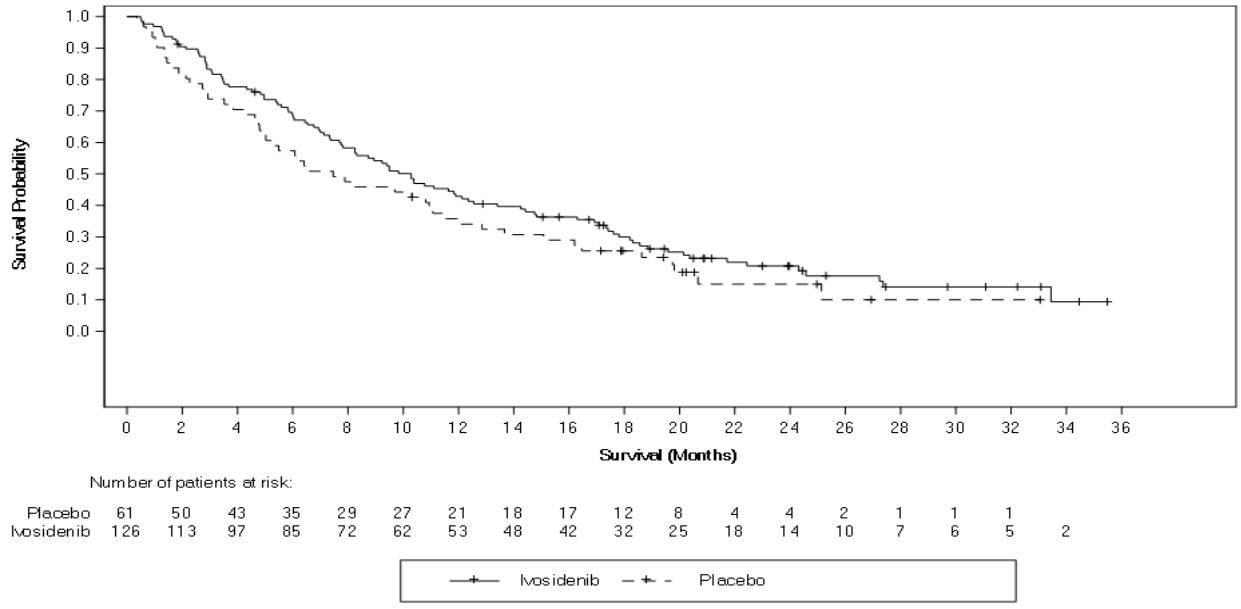


Figure 3: Kaplan-Meier Plot of Overall Survival



15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Safety pharmacology

The potential of ivosidenib for QT prolongation was evidenced in in vitro and in vivo preclinical studies at clinically relevant plasma levels.

Repeat-dose toxicity

In animal studies at clinically relevant exposures, ivosidenib induced haematologic abnormalities (bone marrow hypocellularity, lymphoid depletion, decreased red cell mass together with extramedullary haematopoiesis in the spleen), gastrointestinal toxicity, thyroid findings (follicular cell hypertrophy/hyperplasia in rats), liver toxicity (elevated transaminases, increased weights, hepatocellular hypertrophy and necrosis in rats and hepatocellular hypertrophy associated with increased liver weights in monkeys) and kidney findings (tubular vacuolation and necrosis in rats). Toxic effects observed on haematologic system, GI system and kidney were reversible whereas the toxic effects observed on liver, spleen and thyroid were still observed at the end of the recovery period.

Carcinogenicity:

Carcinogenicity studies have not been conducted with ivosidenib.

Genotoxicity:

Ivosidenib was not mutagenic or clastogenic in conventional in vitro and in vivo genotoxicity assays.

Reproductive and Developmental Toxicology:

Fertility studies have not been conducted with ivosidenib. In the 28-day repeat dose toxicity study in rats, uterine atrophy was observed in females at non-tolerated dose levels approximately 1.7-fold the clinical exposure (based on AUC) and was reversible after a 14-day recovery period. Testicular degeneration was observed in males at non-tolerated dose levels approximately 1.2-fold the clinical exposure (based on AUC) in animals prematurely euthanized.

In embryofoetal development studies in rats, lower foetal body weights and delayed skeletal ossification occurred in the absence of maternal toxicity. In rabbits, maternal toxicity, spontaneous abortions, decreased foetal body weights, increased post implantation loss, delayed skeletal ossification and visceral development variation (small spleen) were observed. Animal studies indicate that ivosidenib crosses the placenta and is found in foetal plasma. In rats and rabbits, the no adverse effect levels for embryofoetal development were 0.4-fold and 1.4-fold the clinical exposure (based on AUC), respectively.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTIBSOVO®
Ivosidenib Tablets

Read this carefully before you start taking **TIBSOVO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TIBSOVO.**

Serious Warnings and Precautions

Differentiation syndrome in patients with acute myeloid leukemia (AML):

TIBSOVO can cause a serious condition known as **differentiation syndrome** in patients with AML. This is a condition that affects your blood cells and may be life-threatening if not treated.

Seek urgent medical attention if you have any of the following symptoms after taking TIBSOVO:

- fever
- cough
- trouble breathing
- rash
- decreased urination
- dizziness or light-headedness
- rapid weight gain
- swelling of your arms or legs

These may be signs of differentiation syndrome. Differentiation syndrome in patients with AML happened up to 33 days after starting TIBSOVO.

A patient alert card is included in the packaging for TIBSOVO that tells you and your healthcare professionals about differentiation syndrome as well as the symptoms that you may experience. Carry this card with you at all times. Be sure to keep it in a safe place. Show this card to any healthcare professional involved in your care so that they know you are taking TIBSOVO.

Heart Problems:

TIBSOVO can cause a serious heart condition known as QTc interval prolongation. This can cause irregular heartbeats and life-threatening arrythmias (abnormal electrical activity of the heart that affects its heartbeat or rhythm).

Seek urgent medical help immediately if you feel dizzy, light headed, abnormal heartbeat (palpitations) or faint after taking TIBSOVO.

Tell your health professionals you are taking TIBSOVO before starting any new medicines as these may increase the risk of an abnormal heartbeat.

Your health professional will check the electrical activity of your heart before and during treatment with TIBSOVO.

If necessary, your health professional may lower, temporarily hold, or permanently stop your treatment with TIBSOVO.

What is TIBSOVO used for?

TIBSOVO is used to treat adults with:

- acute myeloid leukemia (AML). This is a cancer of the white blood cells.
    - For these patients, TIBSOVO is used with another anti-cancer medicine called "azacitidine".
- bile duct cancer (also known as "cholangiocarcinoma"). This is a cancer of the bile ducts (tubes that carry bile from your liver to your intestine)
    - TIBSOVO is used on its own to treat patients whose bile duct cancer has spread to other parts of the body (metastatic cancer) and who have been treated with at least one prior medicine.

TIBSOVO is only used in patients whose AML or bile duct cancer is related to a change (mutation) in the IDH1 protein.

How does TIBSOVO work?

TIBSOVO contains ivosidenib. It is a medicine used to treat specific cancers that contain a mutated (changed) gene that makes a protein called IDH1. This protein helps make energy for cells. When the IDH1 gene is mutated, the IDH1 protein is changed and does not function properly. This results in changes in the cell which can lead to cancer. TIBSOVO blocks the mutated form of the IDH1 protein and helps to slow or stop the cancer from growing.

What are the ingredients in TIBSOVO?

Medicinal ingredient: Ivosidenib

Non-medicinal ingredients: Colloidal silica (anhydrous), Croscarmellose sodium, Hypromellose acetate succinate, Magnesium stearate, Microcrystalline cellulose, Sodium lauryl sulfate, Hypromellose, Indigo carmine aluminum lake, Lactose monohydrate, Titanium dioxide, Triacetin.

TIBSOVO comes in the following dosage forms:

Tablets: 250 mg

Do not use TIBSOVO if:

- you are **allergic** to **ivosidenib** or any of the **other ingredients** of this medicine.
- you are already taking medicines such as:
    - St. John's wort (a herbal product used for depression and anxiety).
    - rifampicin (used for treating bacterial infections).
    - medicines used to treat epilepsy (a condition where you have recurring seizures) like carbamazepine, phenobarbital, phenytoin.
- you have a heart problem that you were born with called "congenital long QTc syndrome". This is a condition that causes fast and irregular heartbeats.
- you have a familial history of sudden death or an abnormal or irregular heartbeat in the lower chambers of the heart.
- you have a severe abnormal electrical activity of the heart that affects its rhythm. This is a condition called 'QTc prolongation'.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TIBSOVO. Talk about any health conditions or problems you may have, including if you:

- have heart problems or have a family history of heart problems.
- have been told by your healthcare professional before that you have abnormal levels of electrolytes (such as sodium, potassium, calcium or magnesium).
- are taking certain medicines that can affect the heart such as:
    - medicines used treat abnormal heartbeats (anti-arrhythmics),
    - medicines used treat bacterial infections (antibiotics) or fungal infections (antifungals)
    - medicines used to prevent nausea and vomiting.
- have kidney problems.
- have liver problems.
- suffer from a lactose intolerance. This is because TIBSOVO contains lactose.
- are pregnant, may become pregnant, or have a partner who is pregnant. TIBSOVO may harm your unborn baby.
    - Women who might become pregnant or men with partners who might become pregnant must use effective birth control to avoid pregnancy during treatment with TIBSOVO and for at least 1 month after the last dose.
    - **Talk to your healthcare professional about the right birth control method for you and your partner.**
    - Tell your healthcare professional right away if you are pregnant, become pregnant, think you may be pregnant or want to get pregnant, while taking TIBSOVO.
- are breast-feeding. Do NOT breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose. It is not known if TIBSOVO passes into breast milk.

Other warnings you should know about:

Children and adolescents:
TIBSOVO is NOT for use in patients under the age of 18 years of age. There is no information on its use in this age group.

Check-ups and testing:
You will have regular visits with your healthcare professional during treatment with TIBSOVO to monitor your health. They will:

- do blood tests before you start and during treatment with TIBSOVO.
- check for signs and symptoms of heart problems.

Your healthcare professional will check the electrical activity of your heart before and during treatment with TIBSOVO.

- You will be given an electrocardiogram (ECG – a recording of the electrical activity of your heart) to monitor your heartbeat before you start treatment with TIBSOVO, once a week for the first three weeks of treatment, and then monthly thereafter.
- Additional ECGs may be given as if required, by your healthcare professional.
- If you start taking certain medicines that can affect your heart, you will be given an ECG before starting and during treatment with the new medicine, as needed.

Driving and using machines:
TIBSOVO may affect your ability to drive or use any tools or machines. If you feel unwell after taking

TIBSOVO, do not drive or use any tools or machines until you feel well again.

Pregnancy, breast-feeding and fertility:
TIBSOVO is NOT recommended to be used in women who are pregnant. TIBSOVO may harm the unborn baby.

Women who are able to get pregnant should have a pregnancy test done before starting treatment with TIBSOVO and should avoid becoming pregnant during treatment.

Tell your healthcare professional right away if you are pregnant, become pregnant, think you may be pregnant or want to get pregnant, during your treatment with TIBSOVO.

Women who might become pregnant or men with partners who might become pregnant must use effective birth control to avoid pregnancy during treatment with TIBSOVO and for at least 1 month after the last dose.

- TIBSOVO may stop hormonal birth control drugs from working properly.
- If you or your partner use birth control pills, contraceptive patches, implants or other hormonal birth control drugs, you must also use a barrier method (such as condoms or a diaphragm) to avoid becoming pregnant.
- Talk to your healthcare professional about the right birth control method for you and your partner.

Do NOT breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose. It is not known if TIBSOVO passes into breast milk.

It is not known if TIBSOVO impacts your ability to have children (fertility). Talk to your healthcare professional if you are concerned about your fertility while taking TIBSOVO.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TIBSOVO:

- antibiotics used for bacterial infections like erythromycin, clarithromycin, ciprofloxacin, levofloxacin.
- warfarin (used to prevent blood clots).
- medicines used for fungal infections like itraconazole, ketoconazole, fluconazole, isavuconazole, posaconazole, voriconazole.
- medicines that affect your heartbeat (anti-arrhythmics) like diltiazem, verapamil, quinidine.
- medicines used to stop nausea and vomiting (anti-emetics) like aprepitant, ondansetron, tropisetron, granisetron.
- medicines used after organ transplants (immunosuppressants) like ciclosporin, everolimus, sirolimus, tacrolimus).
- medicines used to treat HIV (human immunodeficiency virus) like ritonavir.
- alfentanil (used for anaesthesia in surgery).
- fentanyl (used for severe pain).
- pimozide (used for schizophrenia).

- medicines used for cancer like cyclophosphamide, ifosfamide, paclitaxel.
- methadone (used for morphine or heroin addiction, or severe pain).
- medicines used for type 2 diabetes like pioglitazone, repaglinide.
- omeprazole (used for stomach ulcers and acid reflux).
- furosemide (used for fluid build-up known as edema).
- medicines used for high cholesterol known as statins like atorvastatin, pravastatin, rosuvastatin.
- lamotrigine (used for epilepsy).
- hormonal contraceptives (used for birth control).
- grapefruit and grapefruit juice.

How to take TIBSOVO:

- Always take this medicine exactly as your healthcare professional has told you and check with him if you are not sure.
- Take the tablets orally once a day at about the same time each day.
- Do not eat anything for 2 hours before taking TIBSOVO and until 1 hour after taking TIBSOVO.
- Swallow the tablets whole with water.
- If you vomit after taking your usual dose, do NOT take additional tablets. Take your next dose as usual the following day.
- Your healthcare professional may lower, temporarily hold, or permanently stop your treatment with TIBSOVO if you experience certain side effects.
- Do NOT stop taking TIBSOVO before discussing it with your healthcare professional first.

Usual dose:

- Take two 250 mg tablets (500 mg TIBSOVO) by mouth, once a day, at about the same time each day.
- Your healthcare professional may tell you to take one tablet (250 mg TIBSOVO) if you are taking some other medicines or to help you better tolerate some possible side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much TIBSOVO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of TIBSOVO, take the tablets as soon as possible unless the next dose is to be taken within 12 hours.
- Do **NOT** take two doses of TIBSOVO within 12 hours.
- Take the next dose as usual the following day.

What are possible side effects from using TIBSOVO?

These are not all the possible side effects you may feel when taking TIBSOVO. Some of these side effects may occur when taking TIBSOVO or when taking TIBSOVO with azacitidine. If you experience any side effects not listed here, talk to your healthcare professional.

The side effects of TIBSOVO when used in combination with azacitidine in adults with AML include:

- low levels of blood platelets which can lead to bleeding and bruising (thrombocytopenia)
- high levels of white blood cells (leukocytosis)
- low levels of white blood cells (leukopenia)
- difficulty sleeping (insomnia)
- headache
- dizziness
- nerve damage in arms and legs causing pain or numbness, burning and tingling (peripheral neuropathy)

The side effects of TIBSOVO in adults with Cholangiocarcinoma include:

- fatigue
- nausea
- abdominal pain
- diarrhea
- decreased appetite
- a build-up of fluid in the abdomen (ascites)
- low levels of red blood cells (anemia)
- headache
- nerve damage in arms and legs causing pain or numbness, burning and tingling (peripheral neuropathy)
- rash
- increased breakdown product of red blood cells (blood bilirubin) which can cause yellowing of the skin and eyes
- changes in liver function tests (aspartate aminotransferase and alanine aminotransferase increased)
- white blood cell count decreased
- platelet count decreased
- build-up of bile causing yellowing of the skin or eyes (jaundice cholestatic)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Differentiation syndrome: fever, cough, trouble breathing, rash, decreased urination, dizziness or light headedness, rapid weight gain, swelling of your arms and legs			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Heart rhythm problems (QTc interval prolongation): dizzy, lightheaded, faint.			✓
Vomiting		✓	
Neutropenia (low levels of neutrophils, a type of white blood cell that fights infections): fatigue, fever, aches, pains and flu-like symptoms		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15°C to 30°C).
- Do not use this medicine after the expiry date which is stated on the bottle label and box.
- Keep out of reach and sight of children.
- Keep the bottle tightly closed in order to protect from moisture.

If you want more information about TIBSOVO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.servier.ca), or by calling 1-800-363-6093.

This leaflet was prepared by Servier Canada Inc.

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